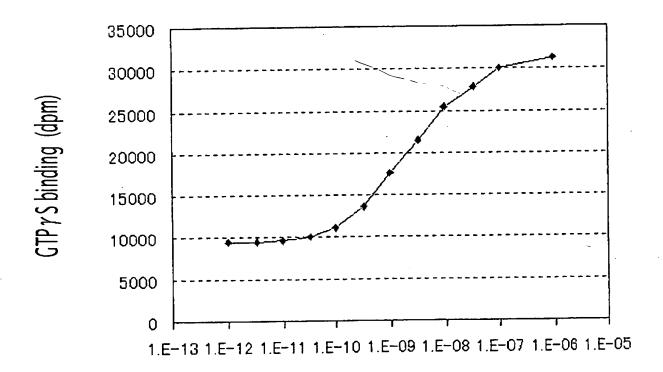


Fig. 2



GPR 8 ligand [M]

Fig. 3

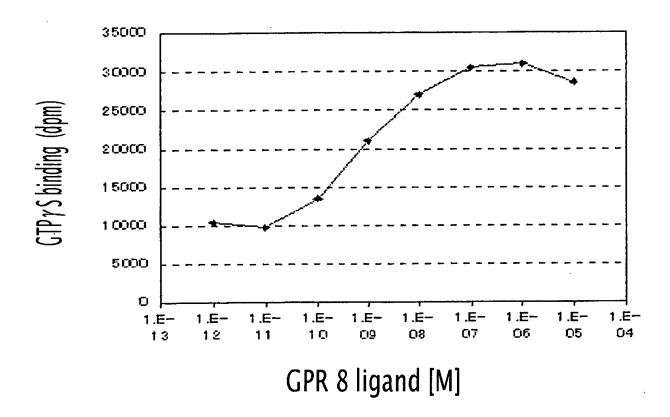
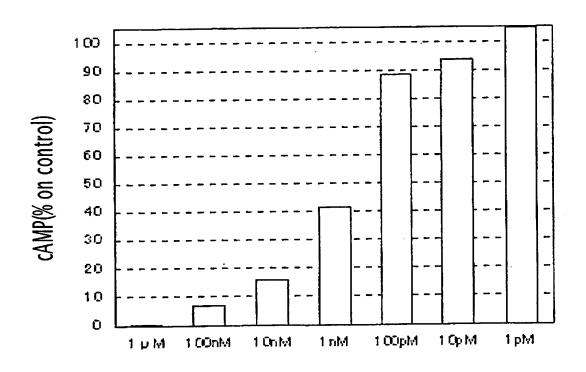
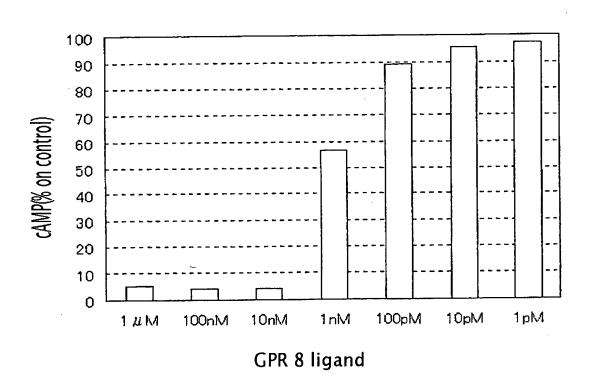


Fig. 4



GPR 8 ligand

Fig. 5



						GGC	GGG	GCC	VCC	GAG	CGG	ATT	TAG	CTG	GGC	CTG	CAG	GGG	ACC	42
- ^ C	ccc	ፐርር	ССТ	CCA		TCC														102
-CA	300	100	ccc	GAG	CCG	GTT	CGT	GGC	CCG	CCC	CGC	CGG	GCG	GCC	GTC	GAC	GCG	AGC	GCC	162
JUN	MAC	COA	000	UNU	000	0		•••												
~~	ccc	тес	cec	CCA	GGG	GAG	CGG	GGG	GCT	CCC	GCG	AGC	CGG	CCG	CGG	CTG	GCA	CTG	CTG	222
	410	Twn	420	Pro	Glv	Ġlu	Arg	Glv	Ala	Pro	Ala	Ser	Arg	Pro	Arg	Leu	Ala	Leu	Leu	20
Leu	MIA	114	VIR	,10	O.J.	010	6	,												
ርፕር	СТТ	CTG	СТС	CTG	CTG	CCG	CTG	CCC	TCC	GGC	GCG	TGG	TAC	AAG	CAC	GTG	GCG	AGT	CCC	282
CIU	Len	Len	Lev	Leu	Leu	Pro	Leu	Pro	Ser	Gly	Ala	Trp	Tyr	Lys	His	Val	Ala	Ser	Pro	40
Leu	200	Dog	202																	
CGC	TAC	CAC	ACG	GTG	GGC	CGC	GCC	GCT	GGC	CTG	CTC	ATG	GGG	CTG	CGT	CGC	TCA	CCC	TAT	342
Arg	Tvr	His	Thr	Val	Gly	Arg	Ala	Ala	Gly	Leu	Leu	Met	Gly	Leu	Arg	Arg	Ser	Pro	Tyr	60
CTG	TGG	CGC	CGC	GCG	CTG	CGC	GCG	GCC	GCC	GGG	CCC	CTG	GCC	AGG	GAC	ACC	CTC	TCC	CCC	402
Leu	Trp	Arg	Arg	Ala	Leu	Arg	Ala	Ala	Ala	Gly	Pro	Leu	Ala	Arg	Asp	Thr	Lev	Ser	Pro	80
GAA	CCC	GCA	GCC	CGC	GAG	GCT	CCT	CTC	CTG	CTG	ccc	TCG	TGG	GT1	CAG	GAG	CTG	TGG	GAG	462
Glu	Pro	Ala	Ala	Arg	Glu	Ala	Prp	Leu	Leu	Leu	Pro	Ser	Trp	Val	Glr	ı Glı	Lev	Trp	Glu	100
ACG	CGA	CGC	AGG	AGC	TCC	CAG	GCA	GGG	ATC	CCC	GT(CG7	C GCC	CCC	CGC	G AGO	CCG	CGC	GCC	522
Thr	Arg	Are	, Ar	g Ser	Ser	Glr	Ala	Gly	Ile	Pro	\Va]	Arg	g Ala	Pro	Arg	g Sei	r Pro	Ar _s	, Ala	120
CCA	GAG	CC1	r GCC	CTC	GAA	ccc	GAC	TCC	CTO	GAC	TT	AG(C GG/	A GC	r GG(C CA	G AG/	A CT.	r CGG	582
Pro	Glu	ı Pro	Ala	a Lei	1 Gl	ı Pro	Gli	Se1	Let	ıaA ı	Phe	e Set	r Gl;	y Ala	a Gl	y Gla	n Arg	g Let	ı Arg	140
AGA	GAC	C GT	C TC	C CGC	C CC	A GC(GTO	G GAC	CCC	GC	A GC	A AA	C CG	C CT	T GG	C CT	G CC	C TG	C CTG	642
Arı	g Ası	ya.	l Se	r Ar	g Pro	o Ala	a Val	l Asy	o Pro	Al:	a Ala	a Asi	n Ar	g Le	บ G1	y Le	u Pro	э Су	s Leu	160
GC	C CC	C GG.	A CC	G TT	C TG	A CA	G CG	CC(c cc	G CC	C GC	C CG	T GG	C GC	c tc	C GC	G CC	T GA	C CCI	702
	a Pro																			16

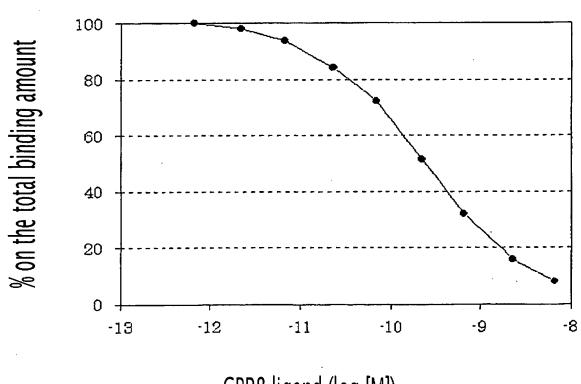
					CC	TCC	GGA	GCC	AGT	TCC	TGG	TCC	GCC	CCG	CCG	GGA	GCC	GTC	AGC	44
ATG	AAC	CCC	CGG	GCA	CGC	GGC	ATG	GGA	GCG	CGG	GGC	CCG	GGA	CCG	GGG	GCC	ACT	GCG	AGG	104
Met	Asn	Pro	Arg	Ala	Λrg	Gly	Met	Gly	Λla	Arg	Gly	Pro	Gly	Pro	Gly	Ala	Thr	Λla	Arg	20
CGC	CGG	CTG	CTG	GCA	TTG	CTG	ATT	CTG	CTG	CTG	CTG	CTG	CCG	CTG	CCC	GCC	CGT	ecc	TGG	164
Arg	Arg	Leu	Leu	Ala	Leu	Leu	Leu	Leu	Lev	Leu	Leu	Leu	Pro	Leu	Pro	Ala	Arg	Ala	Trp	40
TAC	AAG	CAC	ACG	GCG	AGT	CCC	CGC	TAC	CAC	ACG	GTG	GGC	CGC	GCC	GCG	GGC	CTG	стс	ATG	224
Tyr	Lys	His	Thr	Ala	Ser	Pro	Arg	Tyr	His	Thr	Val	Gly	Arg	Ala	Ala	Gly	Leu	Leu	Met	60
GGG	CTG	CGC	CGC	TCG	CCC	TAC	ATG	TGG	CGC	CGC	GCG	CTG	CGC	CCG	GCG	GCC	GGG	ccc	CTG	284
								Trp												80
GCC	TGG	GAC	ACT	TTC	GGC	CAG	GAC	GТG	ccc	ССТ	CGG	GGA	ccc	тсс	ecc	AGG	AAC	GCC	CTC	344
Ala	Trp	Asp	Thr	Phe	Gly	Gln	Asp	Val	Pro	Pro	Arg	Gly	Pro	Ser	Λla	Arg	Asn	Ala	Leu	100
																			TGG	404
Ser	Pro	Gly	Pro	Ala	Pro	Arg	Asp	Ala	Pro	Leu	Leu	Pro	Pro	Gly	Val	Gln	Thr	Leu	Trp	120
CAG	GTG	CGA	CGC	GGA	AGC	TTC	CGC	TCC	GGG	АТС	CCG	GTC	AGT	. ece	ccc	CGC	AGC	cce	CGC	464
Gln	Val	Arg	Arg	Gly	Ser	Phe	Arg	Ser	Gly	Ile	Pro	Val	. Ser	[sA	Pro	Arg	Ser	Pro	Arg	140
GCC	: CGG	GGG	TCC	GAG	cce	CAA	cce	G GAA	TTO	GGC	c GCC	тст	TC	TGC	ACC	с тсс	GCC	G GAG	TAG	524
Ala	Arg	Gly	Ser	Glu	Pro	Glr	Pro	Glı	ı Lei	Gly	/ Ala	Sei	r Sei	Tr	Th	r Sei	. Ala	Glu) ***	159
ACC	C AGA	GC	C TTC	C GGA	A GAO	TC1	r TC/	A GC	r cac	G CGC	G TGC	TC	r GC							568

								TGT	AGT	CGC	ACC	AAC	TGA	CTA	GTC	TCT	TCC	ATC	CTC	36
CGG	AGC	TCC	GAC	GTT	стс	GGG	GAC	ATA	AAC	CCT	GTT	CTT	GTC	CTA	ACC	CGC	САА	GGG	GCC	96
ЛТG	GAC	TTG	AGC	GCG	CTG	GCG	TCG	ΛGC	AGA	GAA	GTA	CGG	GGC	ССТ	GGG	ссс	GGG	GCT	CCG	156
Met	Asp	Leu	Ser	Ala	Leu	Ala	Ser	Ser	Arg	Glu	Val	Arg	Gly	Pro	Gly	Pro	Gly	Ala	Pro	20
GTG	AAC	CGG	CCC	CTG	СТА	CCG	CTA	CTG	CTG	CTT	CTG	СТС	TTG	CTA	сст	CTG	ccc	GCC	AGC	216
Val	Asn	Arg	Pro	Leu	Leu	Pro	Leu	Lev	Pro	Lev	Pro	Ala	Ser	· 40						
						GCG														276
Ala	Trp	Tyr	Lys	His	Val	Ala	Ser	Pro	Arg	Tyr	His	Thr	Val	Gl y	Arg	Ala	Ser	Gly	Leu	60
CTC	ATG	GGG	CTG	ccc	CGC	TCG	ccc	TAC	CTG	TGG	CGC	CGT	GCC	TTG	GGT	GGG	GCC	GCT	GGA	336
Leu	Met	Gly	Leu	Arg	Arg	Ser	Pro	Tyr	Leu	Trp	Arg	Arg	Ala	Leu	Gly	Gly	Ala	Ala	Gly	80
CCG	стс	GTG	GGG	СТС	CCG	GGA	CAG	ATG	GCC	CGC	AGC	GCT	СТС	CTG	CT T	ССТ	тсс	CCC	GGG	396
Pro	Leu	Val	Gly	Leu	Pro	Gly	Ģln	Met	Ala	Arg	Ser	Ala	Leu	Leu	Leu	Pro	Ser	Pro	Gly	100
CAG	GAG	CTG	TGG	GAG	GTA	CGA	AGC	AGG	AGT	TCA	CCG	GCA	GGA	CTT	ссс	GTG	CAT	GCA	ACC	456
Gln	Glu	Leu	Trp	Glu	Val	Arg	Ser	Arg	Ser	Ser	Pro	Ala	Gly	Leu	Pro	Val	His	Ala	Thr	120
CGG	AGT	CTG	CGG	GAC	CTG	GAG	GGA	GCC	GGC	CAA	ССТ	GAG	CAG	TCG	CTA	AGC	TTT	CAG	тсс	516
Arg	Ser	Leu	Arg	Asp	Leu	Glυ	Gly	Ala	Gle	Gln	Pro	Glu	Gln	Ser	Leu	Ser	Phe	Gln	Ser	140
TGG	ACT	TCA	GCA	GAG	CCC	GCT	GCT	AGA	GCC	TTC	GGT	GAG	ACG	CTT	CGT	GCC	CAG	CCA	TGG	576
Trp	Thr	Ser	Ala	Glu	Pro	Ala	Ala	Arg	Ala	Phe	Gly	Glu	Thr	Leu	Arg	Ala	Gln	Pro	Trp	160
TTC	CTG	CAG	CAA	ATC	АТС	TTT	GCC	GAT	CCT	GTC	AGG	CTC	GAC	GAC	CGT	стс	AAG	AAC	CGA	636
Phe	Leu	Gln	Gln	Ile	Ile	Phe	Ala	Asp	Pro	Val	Arg	Leu	Asp	Asp	Arg	Leu	Lys	Asn	Arg	180
TGG	CGC	CCC	CGT	GCT	TGA	CCT	AAG	CAG	GAG	CAC	AGC	TTG	TAG	СТС	CAG					684
Trp	Arg	Pro	Arg	Ala	***															185

1. 3. Comment of the second

							ŤGA	CTG	GTC	TCC	ATC	CTC	TGG	AGC	TCC	GAC	GTG	CTC	GII	39
ጉጉ	CCA	ርልሮ	ΑΤА.	٦٨٨	CCA	GTT	CTT	GTC	CTA	ACC	CTC	CAA	GGG	GCA	TTA	GAC	GTG	AGC	GCG	.99
,16	UUA	GAL	MIN	дло	CUA	011	011	0.0	• • • •	•••										
ידר	ccc	ፐሮፕ	4 A C	۸GA	GAA	ATO	CGG	GGC	ССТ	GGG	CCC	GGG	ACT	CCC	AGG	AAC	CGG	CCC	CTG	159
.10	410	101	Acn	Λοπ	Glu	Val	Arg	Glv	Рго	Gly	Pro	Gly	Thr	Pro	Arg	Asn	Arg	Pro	Leu	20
,eu	nia	261	дон	7116	0.0	,	0	•••										_		
ገፐር	ccc	ств	CTG	CTG	CTT	CTG	CTC	TTG	CTA	CCG	CTG	CCC	GCC	AGC	GCC	TGG	TAT	AAG	CAC	219
leu	Prn	Len	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Pro	Leu	Pro	Ala	Ser	Ala	Trp	Tyr	Lys	His	40
GTG	GCG	AGT	CCC	CGC	TAT	CAC	ACA	GTG	GGT	CGT	GCC	TCC	GGG	CTG	CTC	ATG	GGG	CTG	CGC	279
Val	Ala	Ser	Pro	Arg	Tyr	His	Thr	Val	Gly	Arg	Ala	Ser	Gly	Leu	Leu	Met	Gly	Leu	Arg	60
						*														ขอก
CGC	TCG	ccc	TAC	CAG	TGG	CGC	CGT	GCC	CTG	GGC	GGG	GCT	GCT	GGA	CCC	CTC	100	C66	Lau	339 80
Arg	Ser	Pro	Туг	Gli	Trp	Arg	Arg	A)a	leu	Gly	Gly	Ala	Ala	Gly	Pro	ren	261	MIR	Leu	80
							0.05	070	OT C		CCT	ፐርር	ተቦል	ccc	CAG	GAG	СТС	TGG	GAG	399
CCA	GGA	CCG	GT(CCC	CGC	GGC	GCT	CIC	616	i tii	Dro	100 207	Ser	Glv	Gla	Gli	Lev	Trp	Glu	100
Pio	Gly	Pro	Val	Ala	a Arg	, 613	818	Leu	Leu	LEI	110	261	501	0,,	011	, 010				
	004	401			C TCA		. CCI	ຕດດ	: CTT	000	GTO	CAT	GCA	CCC	TGC	G AGT	000	CGG	GAC	459
GIA	CGA	AGG	, AUI	יטא נ	r Sei	, Dec	Ala	i Glv	Lev	ı Pro	Val	His	Ala	Pro	Tri	Sei	rPro	Arg	Asp	120
vai	ATE	, se	, WI	g De	1 561	, , , 0	, ,		20.											
стс	CAG	: 66	СТ	n ng	C CA/	A CCG	G GAC	G CAG	TC(G CTA	AGO	CTI	CAC	TCC	; TG(G AT	C TC/	A GAG	GAG	519
len	Gli	. G1:	v Va	0 00 1 At	g Gli	n Pro	G) i	ı Gln	Sei	r Lei	Sei	Lei	ı His	s Ser	Ti	p Ile	e Se	r Glu	G l u	140
ccc	GC1	r GC	T AG	A GC	C TT	C GG/	A GA	G ACC	CT'	r cgi	r GC(CAC	G CC/	A TGC	3 TT	C CT	G CA	G CAA	GTC	579
Pro	Ala	a Al	a Ar	g Al	a Ph	e Gly	y G):	u Thi	r Le	u Ara	g Ala	a Gli	n Pro	o Tri	Ph.	e le	u Gli	n Glī	l Val	160
OTA	TT	r GC	C GA	T CC	T GT	C AG	G CC	C AA	G AA	C CG	A TG	G CG	C CC	C CA	I GC	1 1G	A CC	T AGO	G CAG	639
116	e Pho	e Al	a As	р Рі	o Va] Ar	g Pr	o Ly	s As	n Ar	g Tr	р Аг	g Pr	o Hi	s Al	a **	*			176
					G CT															659

Fig. 10



GPR8 ligand (log [M])

Fig. 11

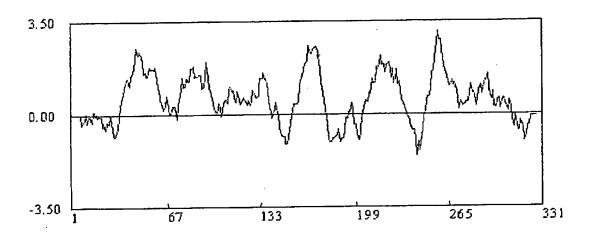


Fig. 12

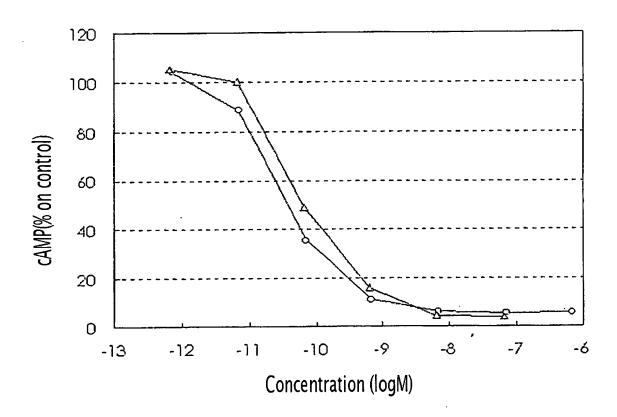


Fig. 13

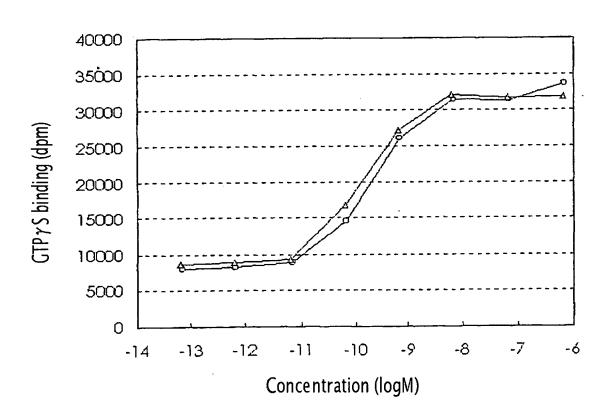


Fig. 14

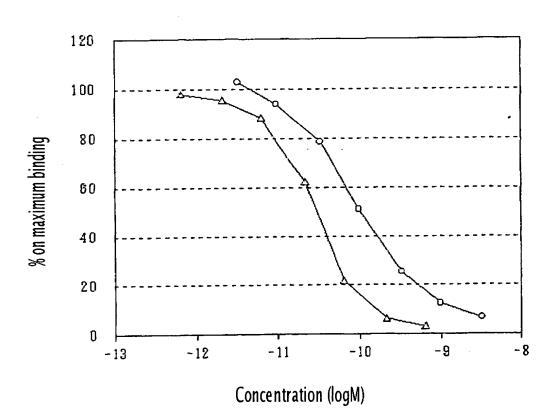


Fig. 15

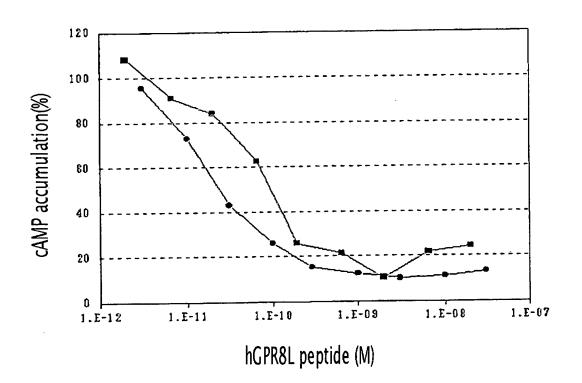


Fig. 16

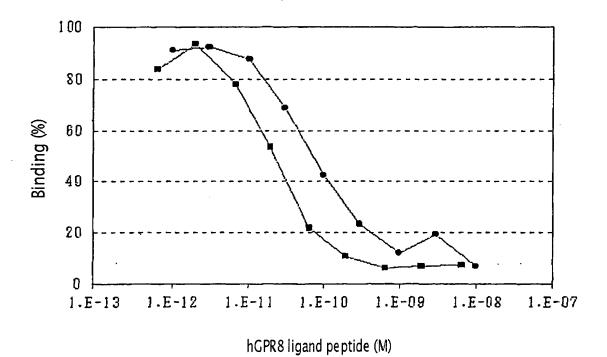


Fig. 17

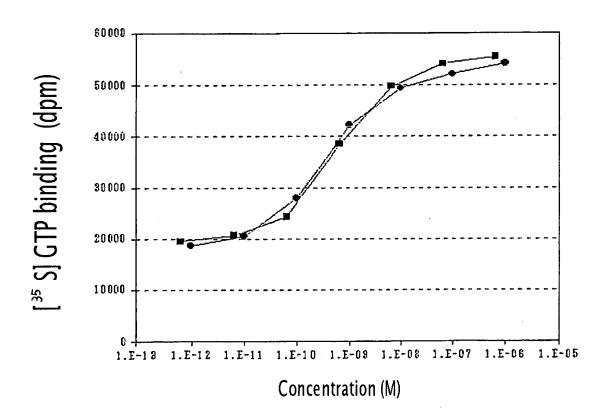


Fig. 18

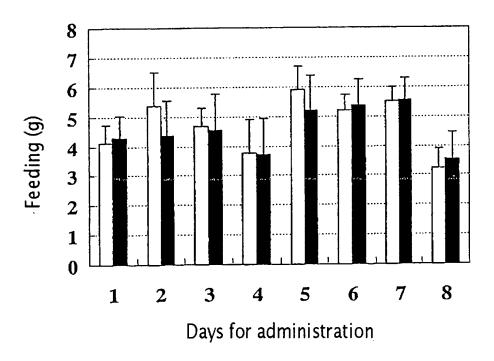


Fig. 19

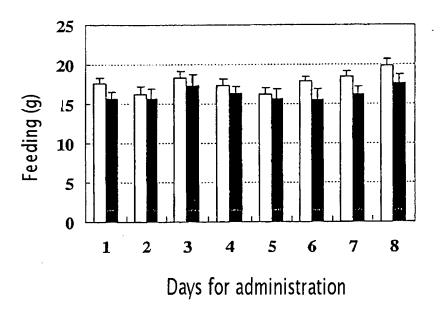


Fig. 20

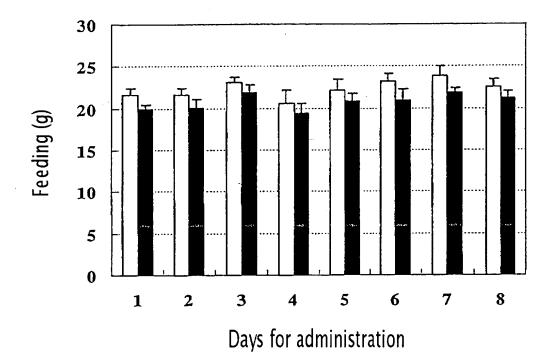
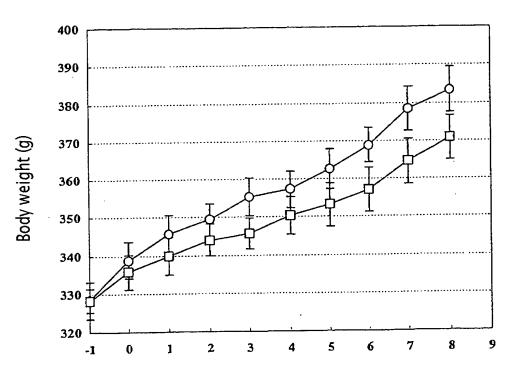
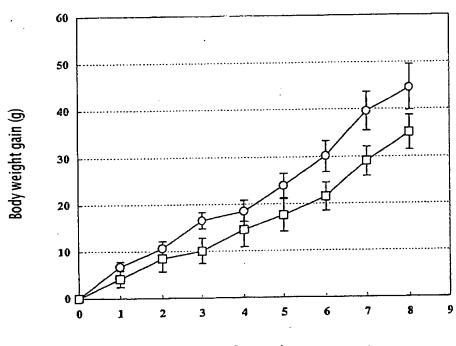


Fig. 21



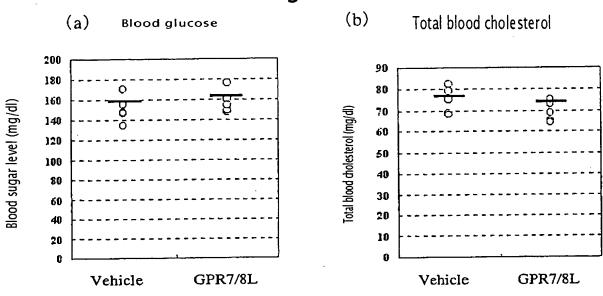
Days for administration

Fig. 22



Days for administration





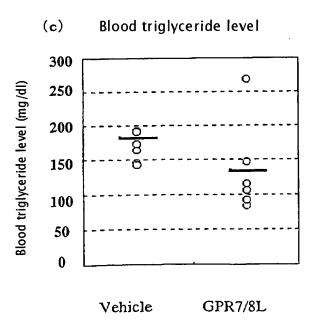


Fig. 24

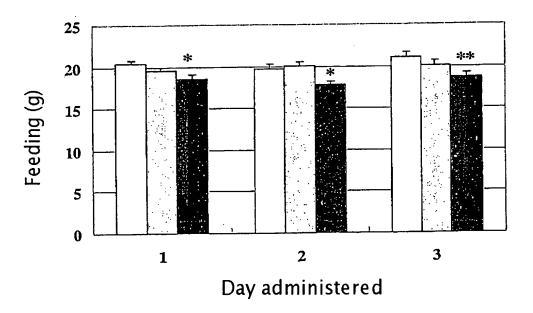


Fig. 25

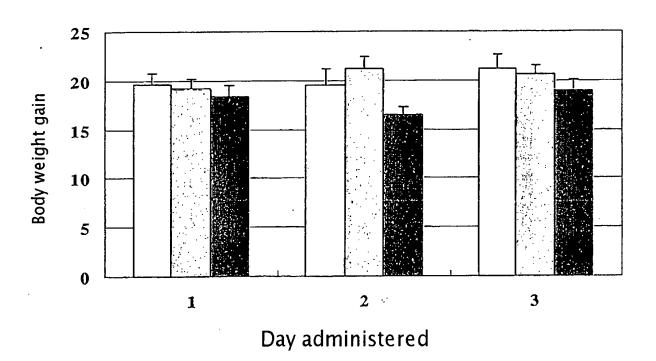


Fig. 26

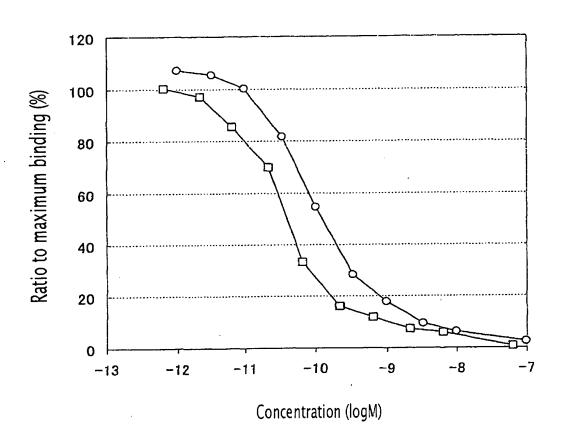


Fig. 27

